MYELOGENOUS LEUKEMIA AND ITS TREATMENT WITH X-RAYS.

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In the last two years there have been 4 cases of myelogenous leukemia observed at the Cooper Medical Clinic, and to these I am adding one seen in private practice. In this same period at the clinic we have seen 1 case of Hodgkin's disease, 1 of Banti's disease, no cases of lymphatic leukemia, no cases of pernicious anemia, and 1 case of anemia with enlarged spleen of doubtful nature. Of some 700 purely medical cases seen yearly at the above clinic, there are 2 or 3 of myelogenous leukemia. As to the etiology, there is nothing positive to say. Two of the patients resided for many years in the malarial districts of California, and still denied ever having had malaria. In only one case was there a history of this infection. Nor were there any other features to which etiological importance could be attached. A history of syphilis was not obtained in any of our patients. All were men varying in age from forty to sixty-two years. Their antecedents and offspring had not suffered from any similar disease. On purely clinical grounds a certain incomplete resemblance to malignant disease was thus seen; this has been commented upon by other observers. The resemblance is further borne out by the course of the disease, its reaction to the *x*-rays, and its occasional improvement by intercurrent infection.

Opinions are divided as to the pathology of the leukemias and Hodgkin's disease. Some regard the processes as essentially hyperplasia, the increased number of leukocytes in the blood, due, in the case of lymphatic leukemia, to the passive washing out of lymphocytes into the blood current, and in myelogenous leukemia to the active migration of various forms of leukocytes following chemotactic influence. More recently these diseases have been regarded as malignant. Atypical growths of cells and a tendency to invade the capsules of the lymph glands and adjacent tissues are the indications of this malignant nature. According to Banti,[1] all leukemias and Hodgkin's disease are really neoplastic. The anatomical changes in the bone marrow, lymph glands, and spleen, where large groups of new cells invade neighboring tissues, are those of sarcomatosis. The walls of the bloodvessels, especially the veins, and even the surrounding bone, are invaded, and the changes in the blood are simply due to the tumor cells gaining entrance to the circulation. If such invaded vessels be thrombosed, the number of leukocytes will drop. In pseudoleukemia such sarcomatous cells have not entered the circulation. When they do, the case becomes clinically one of lymphatic leukemia. Banti regards as true metastases the enormous growths of myeloid or lymphatic tissue in other viscera. Myelogenous leukemia, according to this view, is a systemic myeloid sarcomatosis of the blood and lymph-forming apparatus, while lymphatic leukemia is a systemic lymphadenoid sarcomatosis of these organs. A similar view of malignancy concerning Hodgkin's disease, largely based on anatomical findings, has been expressed by Walter Gibbons.[2]

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[1] Central f. Path. u. path. Anat., January, 1904, Nr. 1.

Clinically, leukemia corresponds closely to malignant neoplastic conditions, and the following clinical factors support the view that it is really a malignant disease: Its onset is insidious. It is practically always fatal. The cachexia of leukemia occurs in the practical absence of fever. It is occasionally benefited by intercurrent affections, a feature true even of such an eminently malignant disease as cancer of the breast. It is usually favorably influenced by the x-rays. Objections based on the rare occurrence of spontaneous recovery in the disease are not very forceful, since similar instances of spontaneous recovery have been observed in undoubted cases of malignancy (Czerny),[3] as, for instance, after incomplete operation, or after intercurrent infection in cancer of the breast. That, in a few recorded cases, a marked hereditary tendency has been noted in leukemia does not harmonize with the usual picture of malignancy. As for the acute leukemias—aside from the blood findings, they do not resemble closely the chronic forms.

Pathologically, the large accumulations of new cells found in the tissues in myelogenous and lymphatic leukemia, pseudoleukemia (Hodgkin's), and chloroma have been differently interpreted. Some pathologists have regarded the picture as essentially that of hyperplasia (Lazarus,[4] Pinkus[5]) occurring in the bone-marrow, lymph glands, and spleen. Others—and I have already cited Banti—believe that the new growths are malignant. In favor of the latter view in myelogenous leukemia is the finding in many organs (lung and liver, for instance) of masses of cells identical with those of bone-marrow, foreign to the particular organs involved, apparently metastases. Growth of this new tissue may also be by direct extension.

In chloroma—green cancer of d'Aran—in which the blood is identical with lymphatic leukemia, this invasive character is particularly marked. Collections of new cells of a greenish color form in and between the bones, especially of the skull and face. By compression blindness, deafness, and various paralyses result. These greenish tumors also occur scattered through the different organs. Stengel[6] calls the disease sarcomatous.

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[2] Amer. Jour. Med. Sci., Nov. 1906.

[3] Zeitschrift f. Krebsforshung, 1907.

[4] Nothnagel's System, 1901.

[5] Ibid.

[6] Text-book of Pathology, 1903.

In lymphatic leukemia the question, too, is how to interpret the new formations. Are they lymphomas of hyperplasia, or are they malignant and sarcomatous?

In another class of cases, however, the combination of leukemia and anemia, called by Leube leukanemia, the resemblance to an acute infection or acute toxemia of rapid onset is striking. Such a case, in which the blood resembled that of a severe leukemia, ending in three and a half months with recovery, was recently described by Teeter[7]. Emerson,[8] in describing 3 cases of acute leukemia, points out the resemblance clinically to an acute infection of the bone-marrow.

SYMPTOMS. These are insidious. One man of our series kept at work seven months after first noticing any disturbance. The first symptoms noted by the patients were dull pains in the left abdomen, and those of anemia, such as weakness, dyspnœa, and pallor. A tumor in the left abdomen was noticed by two of the men. More particularly for the relief of the pain did they go to the physician; this was not severe, so that the first visit was postponed for weeks or months. In 1 case there was also substernal pain. The anemic symptoms were also insidious in onset and had no special characters. In 2 cases there was vomiting and in 2 cases epistaxis. Ringing in the ears and dizziness were the only nervous symptoms noted, and these could also be attributed to anemia. In 3 cases the appetite remained good. In the others it was lessened. The bowels were regular. A loss of weight was usually noted, although it was not excessive. In 1 case this amounted to 19 pounds in two years. One patient was still well nourished. With the progress of the disease the emaciation increased. The skin looked pale, in 1 case it was jaundiced. Arsenical pigmentation and evidence of slight x-ray dermatitis about the splenic region were observed, due to treatment. Slight œdema at the ankles was found in all cases. The pulse, often rapid, was not distinctive. The temperature was elevated at some time in all the cases.

The lungs were found uninvolved in 3 cases. In the fourth case an old tuberculous lesion was overlooked. The fifth case has now a lesion of the right apex, doubtlessly tuberculous. Enlargement of the cardiac dulness transversely occurred in 4 cases. The largest heart extended from the right sternal border to 4 cm. to the left of the left mammary line. A faint systolic murmur was noted occasionally at the apex or base, but in no case was a diagnosis of endocarditis made. Enlargement of hepatic dulness was present in all cases, though the edge of the organ was not always felt. In one case the vertical measurement in the right mammary line was 22 cm. When the liver edge was felt, it was found firm, smooth, and rather rounded. The spleen was enlarged in all cases. In 3 it was enormous, filling out nearly the entire left side of the abdomen, and in these and in a fourth case the splenic tumor was easily seen on inspection of the abdomen. The largest splenic dulness measured 32 x 30 cm., reaching to 6 cm. below the umbilicus and 2.5 cm. to the right of the median line. The organ felt firm, smooth, its edge somewhat rounded and notched more than normally. It was not painful to palpation. The size of the spleen in a general way varied directly with the condition of the patient and with the number of leukocytes, diminishing in size as the patient convalesced and as the leukocytes diminished. Comparing different patients, however, no such parallelism occurred; for instance, in Case I, at a time when there were 632,000 leukocytes per c.mm., the spleen reached at expiration only 4 cm. below the costal margin; while in Case V, with 48,000 leukocytes, the organ extended 6 cm. below the umbilicus. Both of these cases were seen about six months after the first symptoms had appeared. There was slight general enlargement of the lymph glands in Case IV, possibly due to the tuberculous infection subsequently found. In Case III the lymph glands were somewhat enlarged, but not tender. The nervous system and genitalia were negative. The urine in 3 cases showed at first only a trace of albumin, with hyaline and granular casts in 2 cases.

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[7] Jour. Amer. Med. Assoc., February 16, 1907.

[8] Johns Hopkins Hosp. Bull., March, 1907.

Blood. In this series of cases the average number of leukocytes when first seen was 312,000; that of the red cells was 2,860,000. The relation of white to red cells was that of 1 to 9. The average hemoglobin content was 50 per cent. When first seen the myelocytes constituted from 30 to 64 per cent. of all the leukocytes. Under the *x*-rays their numbers were both actually and relatively reduced. Through the influence of an acute miliary tuberculosis in one case they disappeared entirely. The leukocytes in this case dropped from 300,000 to 6000 in five weeks.

This brings up the interesting point of the influence of complicating infections upon leukemia, a subject extensively considered by Dock.[9] From the literature and from his cases, it is shown that, under the influence of complicating infections in leukemic patients, there is a disposition for the leukemic characters of the blood to disappear more or less completely, the spleen, liver, and lymph glands often growing smaller. In the majority of cases the leukocytes are diminished. In about half the cases the number is reduced to normal or less than normal. These conditions hold true for acute infections, in which the number of leukocytes may rapidly diminish within such a short period even as three to ten days. In one of our cases the eosinophilia were absent in several examinations, a feature also noted by Simon. Joachim[10] has recently described 2 cases of what he calls

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[9] Amer. Jour. Med. Sci., April, 1904.

[10] Deutsch. Archiv f. klin. Med., lxxxviii.

"mast-cell leukemia." These mast cells constituted over 50 per cent. of the leukocytes present. It is a variety of myelemia with a prognosis less favorable than the ordinary from. The blood findings in our 5 cases are epitomized in Chart I.

CHART I.—THE BLOOD IN FIVE CASES.

Date.	Red cells.	Hemoglobin.	Leukocytes.	Small mononuclears.	Large mononuclears.	Polynuclears.	Eosinophiles.	Myelocytes.	Basophiles.	Nucleated reds to 500 leukocytes.	Remarks.
Case I.											
Aug. 23, 1905.	2,000,000	30-35	632,000								
Jan. 23, 1906.	3,120,000	60.0	3,400	20.0	10.0	66.7	0.0	3.3	0.0	0.0	Patient doing well.
Apr. 9, 1907.	3,464,000	60.0	85.260	4.6	2.8	69.7	1.8	21.0	0.0	2.0	
Case II.											
Mar. 24, 1905.	4,000,000	67.0	172,000	13.0	10.0	37.0	2.0	31.0	3.0	0.0	Death Sept., 1906
Case III.											
May. 31, 1905.	2,500,000	42.0	570,000	3.0	1.0	30.0	2.0	64.0			
Aug. 21, 1905.	3,650,000	70.0	83,600	4.0	7.5	63.1	1.0	23.9	0.5	7.0	Death Oct. 29, '05
Case IV.											
Nov. 22, 1905.	2,750,000	53.0	160,000	2.5	0.5	40.0	1.5	55.0	1.0	7.0	Miliary tuberculosis
Dec. 26, 1905.	2,220,000	38.0	3,600	4.0	8.0	88.0	0.0	0.0	0.0		Death Jan. 1, '06
Case V.											
Mar. 11, 1907.	3,050,000	55.0	72,000	5.0	3.3	51.7	2.0	30.4	7.6	4.0	Left the wards
Apr. 6, 1907.	3,950,000	60.0	63,600	0.6	1.9	53.3	6.7	37.0	0.6	2 normoblasts.	

DIAGNOSIS. In these cases with a typical blood picture and enlarged spleen the diagnosis was easy. Mixed forms, however, do occur, such as those seemingly combined with pernicious anemia. In lymphatic leukemia the diagnosis is evident by the increase of lymphocytes; myelocytes are not found. In cases of so-called aplastic leukemia, in which the clinical picture of leukemia is present, but with no increase of leukocytes, the diagnosis is based upon the changed blood formula. In an anomalous case studied by Ewald,[11] lasting seven weeks, autopsy findings were identical with myelogenous leukemia, and still the blood gave no sign of it during life.

COURSE AND PROGNOSIS. The prognosis is bad. The disease, in most cases, progresses in spite of treatment and terminal infectious or terminal hemorrhages are likely. Still, with the palliative action of the x-rays the prognosis would seem to be better than formerly. This bad prognosis is exemplified in our 5 cases. In Case III death occurred with anasarca and subdural hemorrhage two and one-half years after the onset of the illness. In Case IV death resulted from miliary tuberculosis nine months after the first symptoms of leukemia. In Case II death ensued two and one-half years after the onset of the first symptoms. Case V has been seen only recently. The patient has been sick for six months, and has at present a catarrh of the right apex, no doubt tuberculous. Case I is remarkable, and will be spoken of especially under treatment. With occasional applications of the *x*-rays for eight months, at the end of a year he had practically recovered. It is now over two years since his symptoms were first noted, and in spite of the fact that he was sixty-two years of age, had a distinctly dilated heart and a good trace of albumin in his urine, with 632,000 leukocytes per c.mm., and with the hemoglobin at 30 to 35 per cent., he is now practically well, able to handle his business interests, and is otherwise strong. The blood picture, however, is far from normal.

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[11] Berliner klin. Woch., xlii, Nr. 26.

TREATMENT. As in other severe chronic conditions, it is imperative that the patient be well fed and receive considerable rest. Our clinic patients were put to bed. They received the regular ward diet, with laxatives as required. Under this careful *regime*, with applications of *x*-rays, they were able to leave the ward, except in one instance, in a few weeks and return to light work. They then received *x*-ray applications once or twice weekly as ambulatory patients. Eventually, as their conditions grew worse, they returned to the ward, with the results previously given. Owing to gastrointestinal irritation, arsenic, either as Fowler's solution or Asiatic pill, was found unsatisfactory. Hypodermic use of arsenic was not tried. By far the most satisfactory results were obtained by giving *x*-rays in small and repeated doses. Except toward the approach of death, the patients grew stronger and the spleen and liver were reduced in size. The leukocytes, especially the myelocytes, were quantitatively reduced. The red cells and the hemoglobin were more difficult to influence. The latter could not be raised to normal; and, even in our most favorable cases, myelocytes were still found.

The method of application of the *x*-rays can be best illustrated by following Case I. Applications were made three times weekly for three months, then every five days for two months, and as the blood picture improved and the patient improved the treatment was given at longer intervals. The current was obtained from a coil; a medium high or medium tube was generally used, occasionally a medium soft; the distance of the tube from the body was 25 to 30 cm; time of exposure, seven to fifteen minutes; amperage, 7 to 10 with the higher tubes; voltage, 10 to 120. Interruptions were made with a Wehnault or mechanical interrupter (2600 to 3000). The regions exposed were the splenic, anteriorly and posteriorly, the dorsal, the two thighs, the epigastric, and the sternal. Dermatitis was carefully avoided. The *x*-ray applications were started three weeks after the patient was first seen. During these three weeks while taking arsenic and iron, he had grown appreciably worse, but with the beginning of the x-ray treatment the improvement began and continued as long as the x-rays were given. This improvement was felt by the patient himself, was found on physical examination, and was particularly striking in the changed blood picture. At the beginning of treatment the blood was as follows: red cells, 2,000,000; white cells, 632,000; hemoglobin, 30 to 35 per cent. Three and a half months afterward the reds were 3,784,000; whites, 8400; hemoglobin, 50 per cent. In September, 1906, five months after the cessation of x-ray applications, the reds were 4,000,000; whites, 10,000; hemoglobin, 70 per cent. A palliative though far less successful effect was shown in three other patients. The number of treatments given monthly with the changed blood picture are tabulated in Chart II. Case IV was complicated by miliary tuberculosis, so that the results were obscured; and in Case V also we believe pulmonary tuberculosis to exist. In Case I the result, as stated, was striking. It was not necessary to place this patient in bed. He lived at home and came to the Lane Hospital for his x-ray applications. Possibly the better result in this case was due partly to the fact that the patient was better able to care for himself, the other 4 being clinic and dispensary patients.[12]

The palliative action of the x-rays in leukemias and pseudoleukemias is now generally conceded. Indicating the profession's interest, Shirmer[13] was able to collect 109 articles on the subject published in two years. We have had no experience with the x-rays in lymphatic leukemia, but in 1 case of Hodgkin's disease, of four years' duration, the general condition of the patient has been much improved and the affected lymph glands made considerably smaller by the x-rays. Most of the good results, however, have occurred in cases of myelogenous leukemia. Cheney[14] has reported one such case, seen at the Lane Hospital. It must be understood distinctly, however, that in the leukemic conditions the x-rays are not curative. They are at most palliative; relapses occur under this as under other methods of treatment, but for several months—over twelve in one of our cases—the patient may be free of symptoms. In a small number of cases, approximately 10 per cent., the treatment seems valueless, or even harmful. The action on the leukocytes may be rapid. After a preliminary rise within a few days or in a few hours there may be a diminution of many thousands. The mononuclears are particularly affected. The red cells and hemoglobin may or may not be increased, but a more definite achievement is the improvement of the patient, as shown by increased appetite, increased

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[12] I acknowledge with thanks the kindness of Dr. Oliver, of the Cooper Pathologica Department, and of Dr. Lehman, of the Cooper Dermatological Department, in furnishing some of these data.

[13] Central. f. d. Grenz. d. Med. u. Chir., ix, 15.

[14] Medical News, 1904

CHART II.—RECORDS OF BLOOD COUNTS WHILE PATIENTS WERE UNDER TREATMENT.

Date.	X-ray applications during the month.	Red cells.	White cells.	Hemoglobin.	Remarks.
Case I.				Per ct.	
Aug. 23, 1905.	3	2,000,000	632,000	30-35	
Aug. 29, 1905.		2,240,000	528,800	40	
Sept. 6, 1905.	13	2,500,000	255,200	40	
Sept. 16, 1905.		2,360,000	245,600	38	
Oct. 4, 1905.	13	3,000,800	360,800	50	
Oct. 24, 1905.		3,160,000	133,600	52	
Nov. 2, 1905.	6	3,550,000	62,400	55	
Nov. 28, 1905.		3,620,000	13,200	60	
Dec. 16, 1905.	6	3,784,000	8,400	60	
Jan. 4, 1906.	6	3,968,000	16,800		Laryngitis of 10 days' duration.
Jan. 28, 1906.		3,120,000	3,400	60	
Feb. 14, 1906.	4	3,440,000	3,000	60	
Mar. 10, 1906.	4	2,820,000	4,600	60	
Apr. 3, 1906.	4	2,400,000	3,600	50	Discontinued *x*-rays after earthquake of 1906.
Sept. 18, 1906.		4,000,000	10,000	70	
Apr. 9, 1907.		3,464,000	85,260	60	
May. 10, 1907.	2	3,536,000	109,100	70	
June 14, 1907.	4	4,100,000	104,800	67	
July 24, 1907.	4	4,100,000	165.000	67	
Case II.					
Apr. 7, 1905.	4	3,960,000	146,000	67	Has been receiving *x*-rays elsewhere; now ambulatory.
Apr. 28, 1905.		4,000,000	100,000	75	
May 3, 1905.	13	4,000,000	97,000	75	
May 24, 1905.		3,750,000	116,000	72	
June 2, 1905.	13	4,000,000	140,000	78	
June 30, 1905.		3,600,000	115,000	74	
July 11, 1905.	13	3,900,000	70,400	76	
July 28, 1905.		4,000,000	54,000	80	
Aug. 16, 1905.	13	4,050,000	41,600	76	
Aug. 24, 1905.		4,000,000	80,000	80	
Sept. 1, 1905.	9	4,250,000	40,000	80	
Sept. 27, 1905.		4,650,000	60,000	82	
Oct. 5, 1905.	13	4,650,000	79,000	80	
Oct. 25, 1905.		4,650,000	56,000	80	
Nov. 9, 1905.	13	3,500,000	54,000	76	Entered Lane Hospital Nov. 30.
Nov. 22, 1905.		3,900,000	64,000	75	
Dec. 7, 1905.	2	3,750,000	40,000	74	Left hospital Dec. 14.
Dec. 27, 1905.		4,000,000	70,400	80	
Jan. 10, 1906.	4	3,500,000	80,000	68	Ambulatory; reëntered Lane Hospital Jan. 19.
Jan. 31, 1906.		3,250,000	90,000	68	
Feb. 12, 1906.	10	3,500,000	104,000	67	Left hospital Feb. 5, reentered Feb. 15.
Feb. 20, 1906.		3,500,000	112,000	65	
Mar. 5, 1906.	13	3,500,000	160,000	63	Left hospital April 16.
Mar. 14, 1906.		3,000,000	160,000	54	X-ray treatment then discontinued.
Apr. 2, 1906.	7	3,000,000	120,000	55	
Apr. 10, 1906.		3,350,000	78,000	64	Death in September.
Case III.					
May 15. 1905.	8	3,150,000	456,000		
May 31, 190[illegible].		2,250,000	510,000	42	
June 12, 1905.	13	2,600,000	460,800	50	Entered Lane Hospital June 28, 1905
June 30, 1905.		2,100,000	563,000	42	
July 11, 1905.	19	2,500,000	540,000	45	
July 19, 1905.		3,000,000	320,000	54	
July 26, 1905.		3,250,000	180,000	60	
Aug. 2, 1905.	15	3,350,000	187,600	62	Left hospital Aug. 16.
Aug. 16, 1905.		3.650,000	104,000	70	
Aug. 30, 1905.		3,500,000	80,000	70	
Sept. 5, 1905.	13	3,650,000	70,000	70	Ambulatory.
Sept. 27, 1905.		3,350,000	136,000	64	
Oct. 12, 1905.	11	2,800,000	260,000	50	Reëntered hospital Oct. 16; death, Oct. 28, '05.
Oct. 25, 1905.		2,600,000	208,000	50	
Case IV.					
Nov. 14, 1905.	3	2,750,000	300,000	50	Entered hospital Nov. 21, 1905.
Nov. 22, 1905.		2,750,000	160,000	53	
Nov. 29, 1905.		3,950,000	160,000	77	
Dec. 7, 1905.	9	2,750,000	40,000	52	Death, Jan. 1, 1906; miliary tuberculosis.
Dec. 21, 1905.		1,850,000	6,000	36	
Dec. 28, 1905.		2,220,000	3,600	38	
Case V.					
Mar. 11, 1907.	4	3,050,000	72,000	55	Entered Lane Hospital, March 19; *x*-rays given first, March 20.
Mar. 22, 1907.		3,100,000	64,000	55	
Mar. 30, 1907.		3,450,000	45,500	60	
Apr. 6, 1907.	3	3,900,000	63,600	60	Left hospital, April 6.

strength and weight, and in women by the reappearance of menstruation. The spleen and liver usually grow smaller.

As to the mode of action of the x-rays, we know that a leukolytic body or bodies develop under treatment. Helber and Linser[15] have shown that serum from an animal treated with x-rays, when injected into another animal, causes a leukopenia. Control serum caused a leukocytosis. The extract of the still living, though extirpated, spleen, which organ had been exposed for several hours to the x-rays, caused a reduction of leukocytes upon being injected into the normal animals. The extract of a control spleen not exposed to the x-rays produced a leukocytosis (Milchner and Wolf[16]). The most convincing work along this line has been done in this country by Capps and Smith.[17] It was proved by them that the serum of leukemic patients improving under x-ray treatment causes a leukopenia when injected into animals; added to a hanging drop of leukocytes from another individual, a disintegration of cells, especially the mononuclears, occurs. They also injected such serum into another leukemic patient not under x-ray treatment and succeeded in demonstrating a rapid and decided drop of leukocytes in the injected patient. With repeated injections, however, a partial immunity to the injected serum was established. Whether this leukolytic substance or substances prevents the excessive formation of leukocytes in the blood and lymph-forming organs, or dissolves the leukocytes after they have been formed, is not known. Nor have the studies of metabolism, especially concerning the uric acid output of patients or animals treated with x-rays, helped to solve the problem. We can, however, say that it has been demonstrated that the blood of leukemic patients and of animals treated by x-rays contains a body or bodies capable of dissolving the leukocytes.

CONCLUSIONS. 1. At present it is best to consider myelogenous leukemia a malignant neoplastic disease.

2. The x-rays are effective in treatment as a palliative measure.

3. The action of the x-rays is associated with the production in the patient of a leukolytic body or bodies.

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[15] Deut. Archiv f. klin. Med., lxxxiii, 1905.
[16] Berliner klin. Woch., xliii, Nr. 23.
[17] Jour. Exp. Med., January, 1907.